

EXHIBIT 42



Understanding Addiction

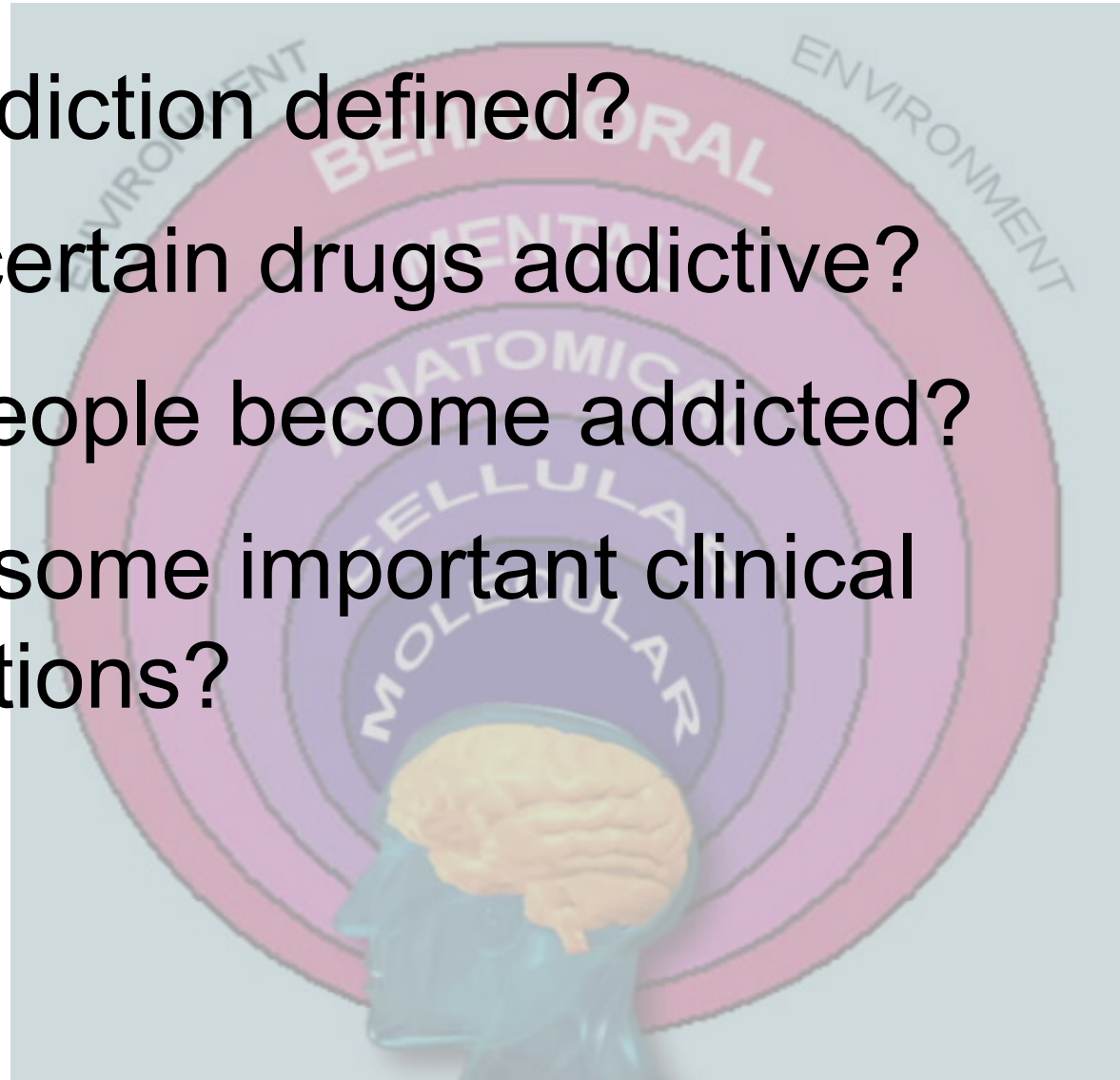
The
Great
Brain
Robbery





What is this presentation about?

- How is addiction defined?
- Why are certain drugs addictive?
- How do people become addicted?
- What are some important clinical considerations?



America “Hooked” on Drugs



Large and growing problems:

- ☐ 6.3 million Americans need treatment for *illicit* substance abuse or addiction.
- ☐ Opioids account for 83% of admissions for injection drug abuse.
- ☐ 4.4 million adults abuse opioid painkillers.
- ☐ 83% of patients entering MMT also abuse Rx opioids.

Better Understandings Essential

- Addiction affects millions of persons.
- Need for science to overcome stigma, prejudice, and misunderstandings.
- Especially important regarding MMT.*

*Methadone Maintenance Treatment.

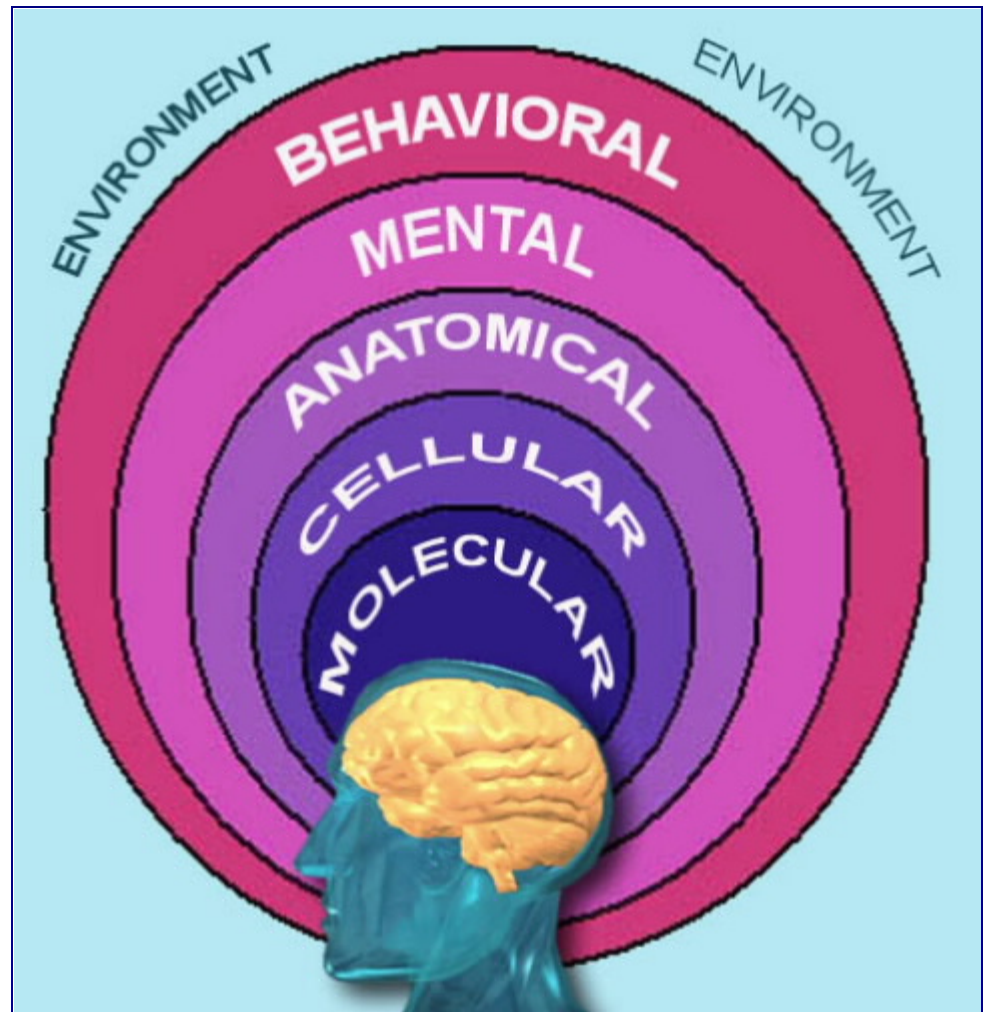


Trepanation once used to release “evil spirits.”

Spheres of Exploration

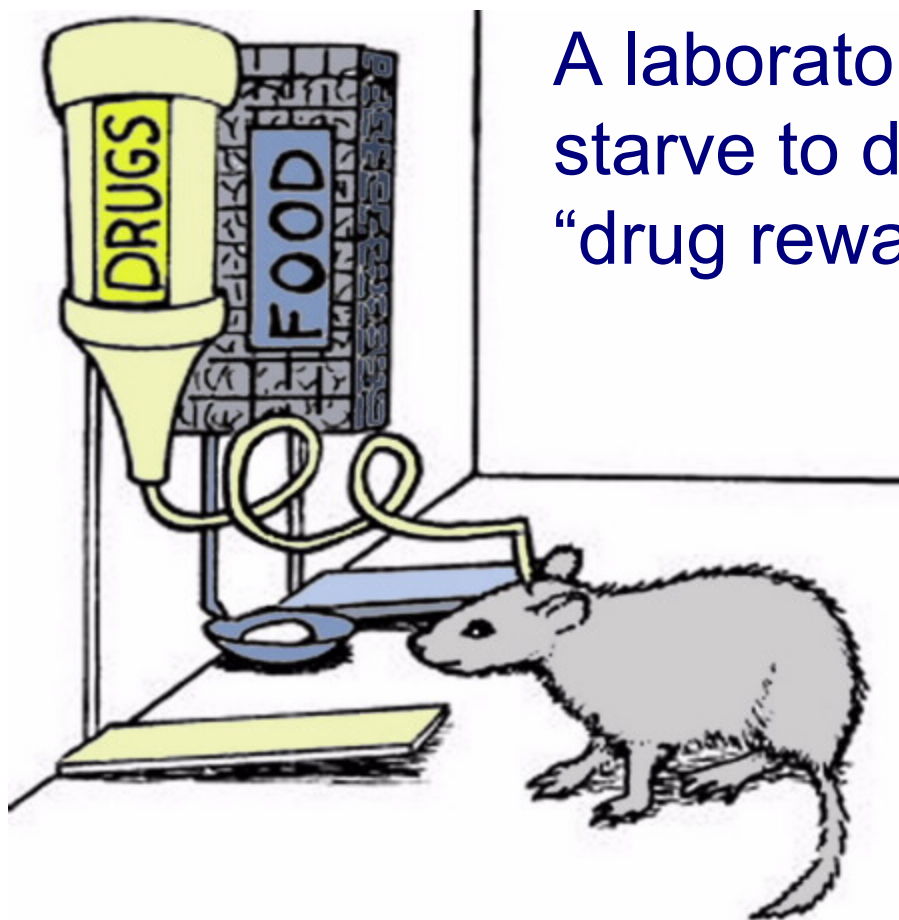
Addiction studied from various perspectives – from actions of molecules in the brain to influences of external environment.

We know a great deal, yet there is much to learn and understand.



A Lab Rat's Life: Food or Drugs?

A laboratory animal will eventually starve to death while seeking only “drug rewards” instead of food.



Drugs can take on survival value that overrides all other, more basic, needs.

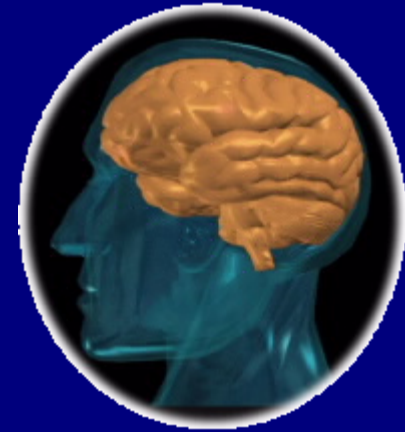
People Have Choices *(Initially)*



- Addiction begins as a voluntary act of drug (or alcohol) taking.
- After repeated use, drugs take control; person is transformed.
- Result is a chronic, relapsing brain disorder – “drug addiction.”



Defining Addiction



**What is the difference
between drug abuse and addiction?**

**How does dependence differ
from addiction?**

**Are drug tolerance and withdrawal
necessary for addiction?**

Misunderstood Definitions

Drug Tolerance*	Reduced drug effects.
Withdrawal*	Abstinence syndrome.
Drug Abuse	Use despite harm.
Drug Addiction	Chronic, relapsing, loss of control.
“Pseudo” Drug Addiction	<i>Inappropriate</i> drug seeking.

* Components of physical *dependence*.

DSM-IV-TR* Criteria — **Drug Abuse**

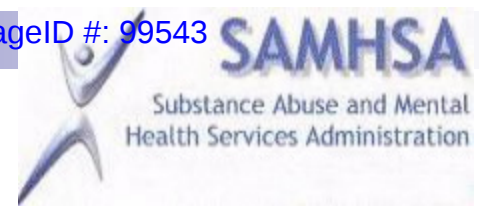
One or more of the following related to drug use:

- Major obligations ignored.
- Use is physically hazardous.
- Substance-related legal problems.
- Social or interpersonal problems.

DSM-VI-TR* — **Drug Dependence**

Three or more of the following related to drug use:

- Tolerance.
- Withdrawal.
- Used more than intended.
- Loss of control.
- Much time/effort expended.
- Important obligations ignored.
- Use despite negative consequences.



MMT Admission Criteria

- Federal MMT Regulations require addiction to an opioid drug.
 - One year, with some exceptions.
- Defined using DSM-IV criteria.

Department of Health and Human Services

Substance Abuse and Mental Health Services Administration

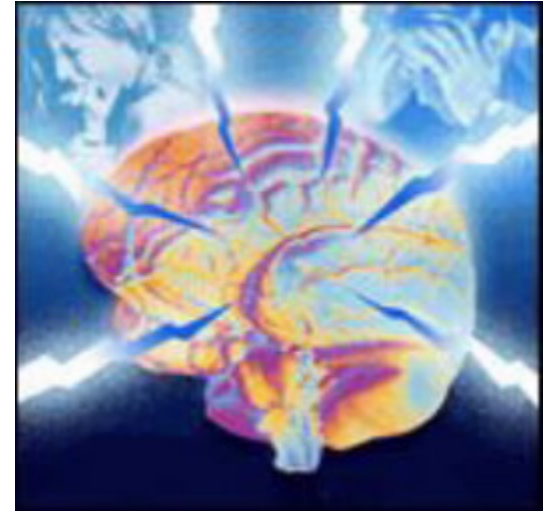
21 CFR Part 291

42 CFR Part 8

Opioid Drugs in Maintenance and Detoxification Treatment of Opiate Addiction; Final Rule

Opioid Addiction Summary

- Cognitive/behavioral aspects take precedence:
 - ☐ Obsessive thinking.
 - ☐ Compulsive use.
 - ☐ Loss of control.
 - ☐ Activities/obligations neglected.
- Physical dependence need not be present – usually is.
- Amount, frequency, type of opioid not critical in defining addiction severity.



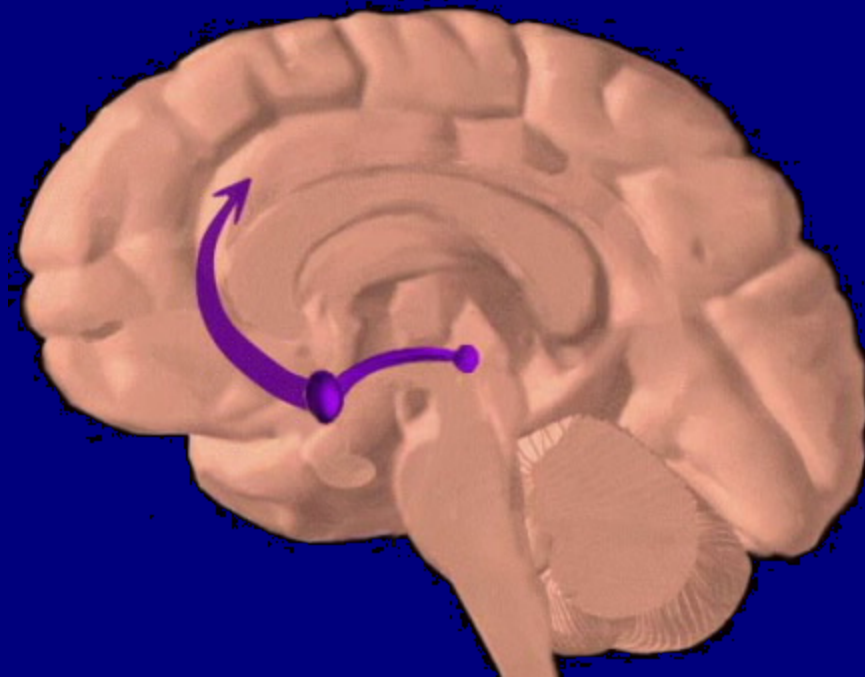
Is Methadone in MMT Addictive?

- Methadone is a prescribed medication, legally dispensed.
- Addictive behaviors replaced by adaptive coping skills.
 - Mental obsession, opioid-seeking cease.
 - Patients engage in normal life activities.
- Patients still physiologically dependent.
 - Withdrawal occurs.
 - Tolerance blocks illicit opioids.





Addiction Pathways in the Brain



It's All About **Dopamine**

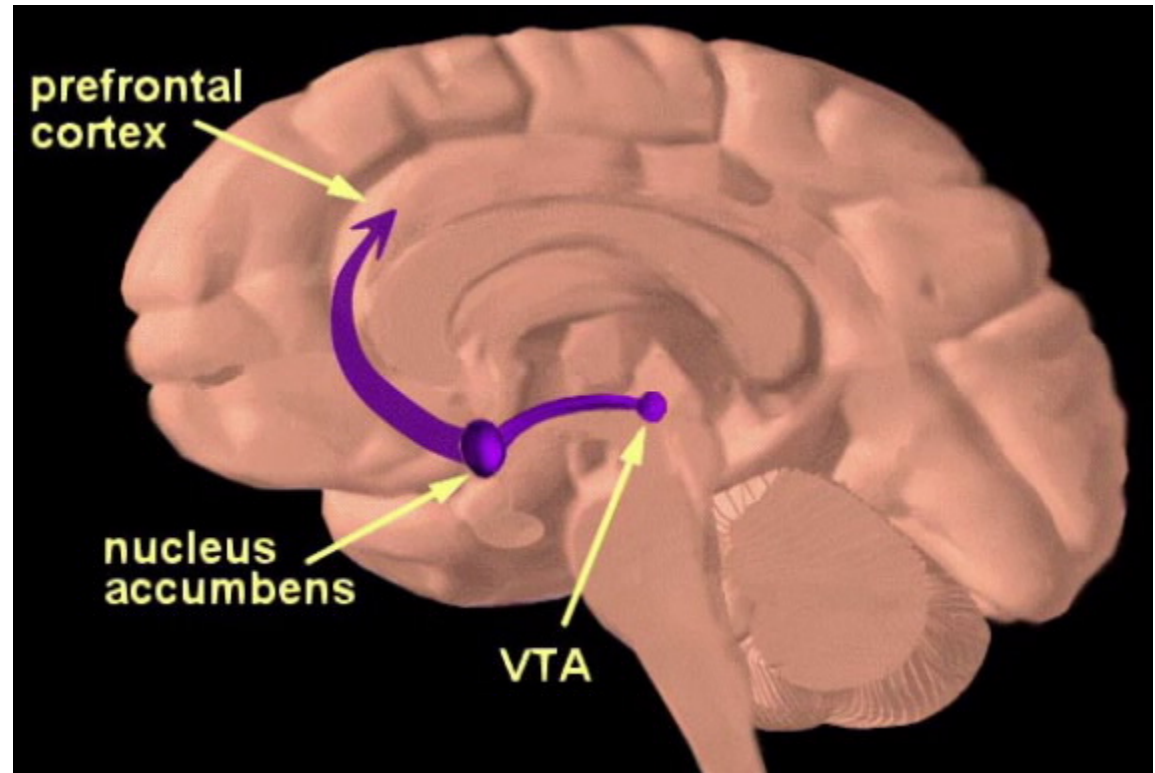
- Dopamine regulates mood/emotions.
- Responsible for motivation, “natural rewards.”
- Addictive drugs stimulate dopamine in brain pathways associated with “reward.”
- In addiction, dopamine system becomes dysfunctional...
 - more drug needed.
 - loss of control over drug use.

The Dopamine-Reward Pathway

Signals travel from VTA (ventral tegmental area) to accumbens.

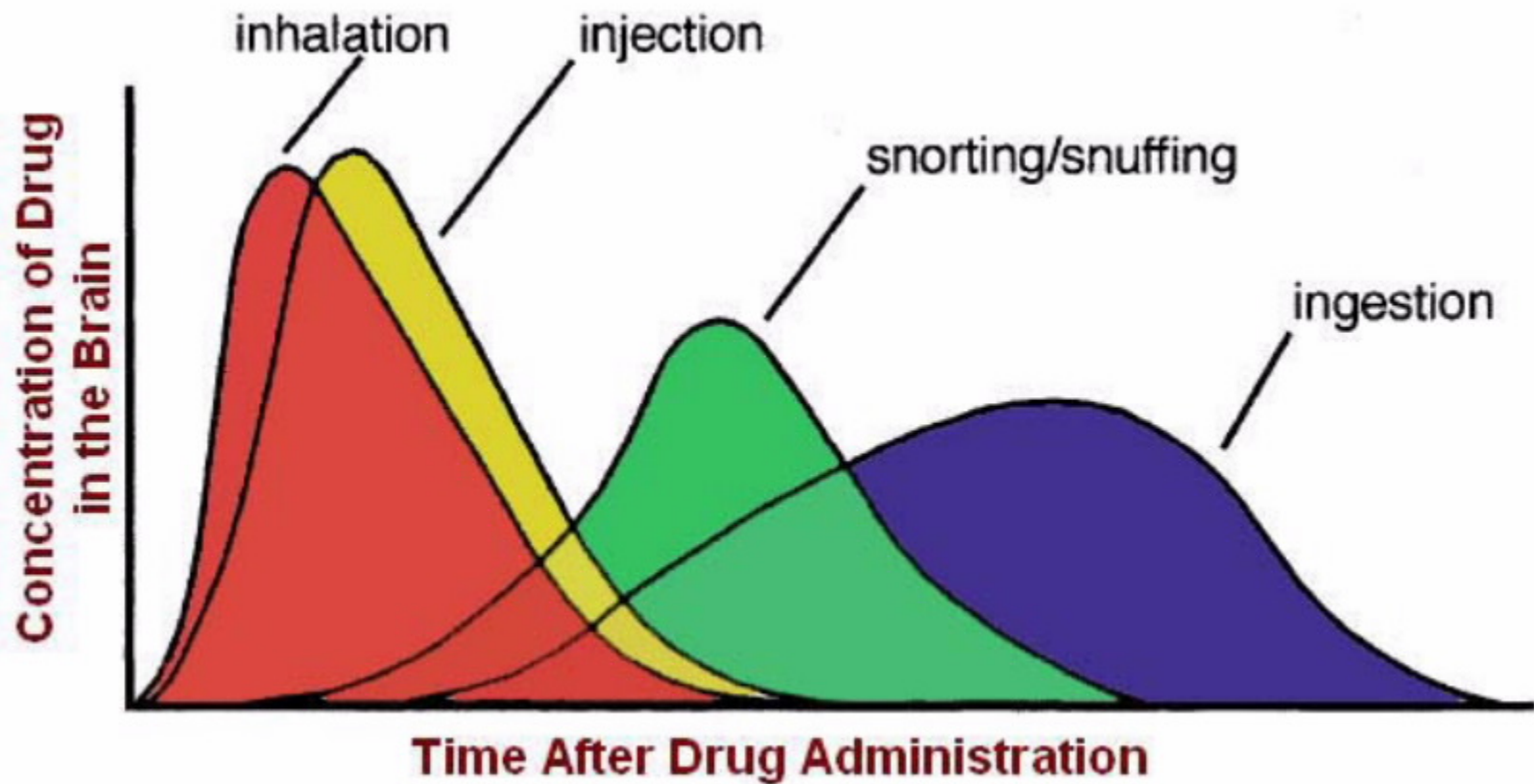
Drug effects can be greater than natural rewards.

Dopamine carries the message.



VTA-accumbens pathway “tells” other brain centers how rewarding a drug is.

Route of Administration Influences Speed & Potency of Drug Effects



“Addiction Switch”

- Abused drugs bypass cognitive (thinking) centers – leads to abnormal brain function.
- As if an “addiction switch” has been turned on – mental world changes, with loss of control unresponsive to individual’s will.
- Intellect is intact, but *volition* – the ability to consciously control drug use – is deranged.
- Brains of addicted persons become “different.”





Some Clinical Considerations

- Diagnosis
- Genetics
- Relapse
- Treatment



Diagnosing Opioid Abuse

- Vein pigmentation, clotted/thrombosed veins.
- Abscesses.
- Clubbing of fingers.
- Constricted pupils.
- Abnormal nasal mucosa.
- Swollen lymph glands.
- Enlarged liver.
- Abnormal lab tests.
- Multiple physicians, vague pain complaints.
- Prior Rx analgesics.
- Blood/urine toxicology.
- Self-reported drug history.

IDU (Injection Drug Use) Skin Lesions



Recent lesions, forearm
–linear skin punctures
("track marks").

New lesions, neck –
inflamed puncture
wounds.



IDU Skin Lesions (continued)



Left hand – old lesions with scars, pigmentation changes, and atrophy (shiny skin); new lesions show healing with fresh scabs.

Right hand – old lesions show inflammatory changes in pigmentation; new lesions show non-healed, inflamed puncture wounds.



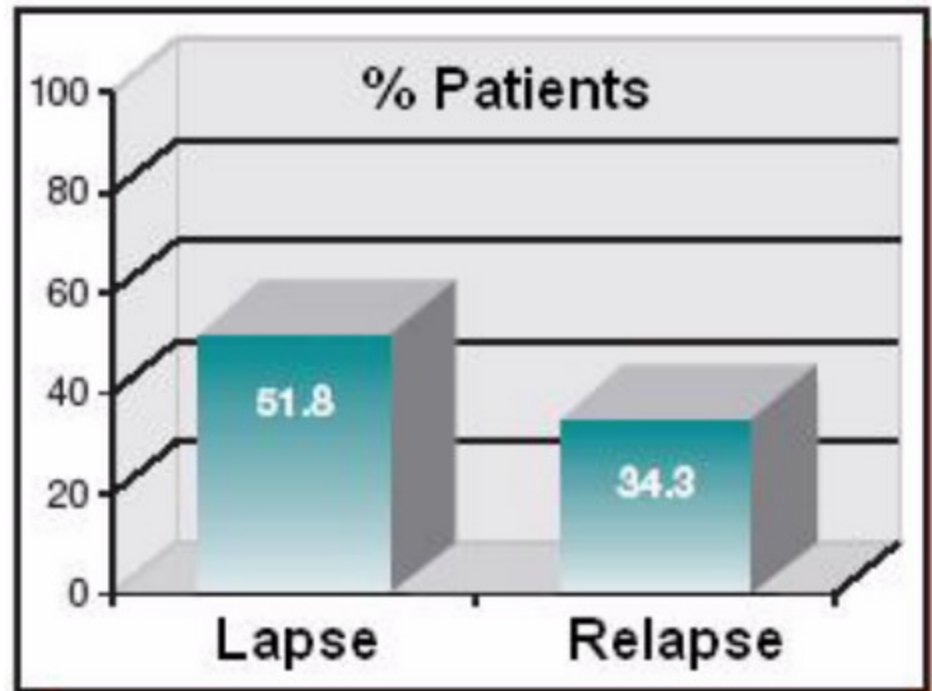
Addiction Genes?

- Genes are involved in addictive processes.
- Some addictions directly influenced by genetics.
- Research still underway.
- Even if genes responsible, they cannot be changed – today.



Is Drug Relapse Avoidable?

- Relapse is a problem of behavior change.
- Several factors contribute.
- Need to “unlearn” drug-related habits and cues.



Can Medications Help?

- Few medications are FDA-approved for addiction treatment.
 - ☐ Methadone
 - ☐ Buprenorphine
 - ☐ Naltrexone
 - ☐ Disulfiram
 - ☐ Acamprosate (approved August 2004)
 - ☐ Methadone is the most thoroughly studied treatment, and has demonstrated effectiveness during 40+ years in millions of MMT patients.



Meds + Psychosocial Therapy Best

Medication Benefits...

- Reduce drug craving.
- Decrease illicit drug use.
- Suppress withdrawal.
- Stabilize brain chemistry.

Therapy Benefits...

- Improve attitudes.
- Reset priorities.
- Therapeutic alliance.
- Develop coping skills.
- Facilitate motivation & compliance.
- Enhance support for sobriety.
- Overcome obstacles to change.
- Create abstinent lifestyle.

Methadose® Brand of Methadone HCl from Mallinckrodt

- Helping to meet the need for flexibility in dosing.
- 5 formulations:
 - Liquid...
 - Cherry (10 mg/mL).
 - Sugar-free, dye-free, unflavored (10 mg/mL).
 - Solid
 - Tablet - 5 mg or 10 mg
 - Dispersible Tab - 40 mg.





Conclusions

- Opioid addiction is a large and growing problem in the U.S.
- Addiction is a chronic, relapsing brain disorder – a disease.
- A principal feature of addiction is dysregulation of the dopamine neurotransmitter system.
- Methadone plus psychosocial therapy are effective treatments for opioid addiction.